Viral Nephropathy Beyond HCV

By

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- **The pathogenetic links between viral infection and renal disease are often difficult to establish.**
- **The criteria for proving causality :**

➢ **1- Recognition of the clinical syndrome.**

➢ **2- Serological diagnosis.**

➢ **3-Identification of specific viral antigenemia.**

➢ **4- Detection in glomerular structures of viral antigens (*n situ* hybridiz tion, polymerase chain reaction and ultra structural analysis)and host antibodies).**

➢ **5- Improvement of the renal disease concomitant with clearance of the suspected antigen, or recurrence of glomerulonephritis following reinfection.**

Mechanisms of Renal Injury

REVIEW
www.nature.com/clinicalpractice/neph

Viral nephropathy

Andrew SH Lai and Kar Neng Lai*

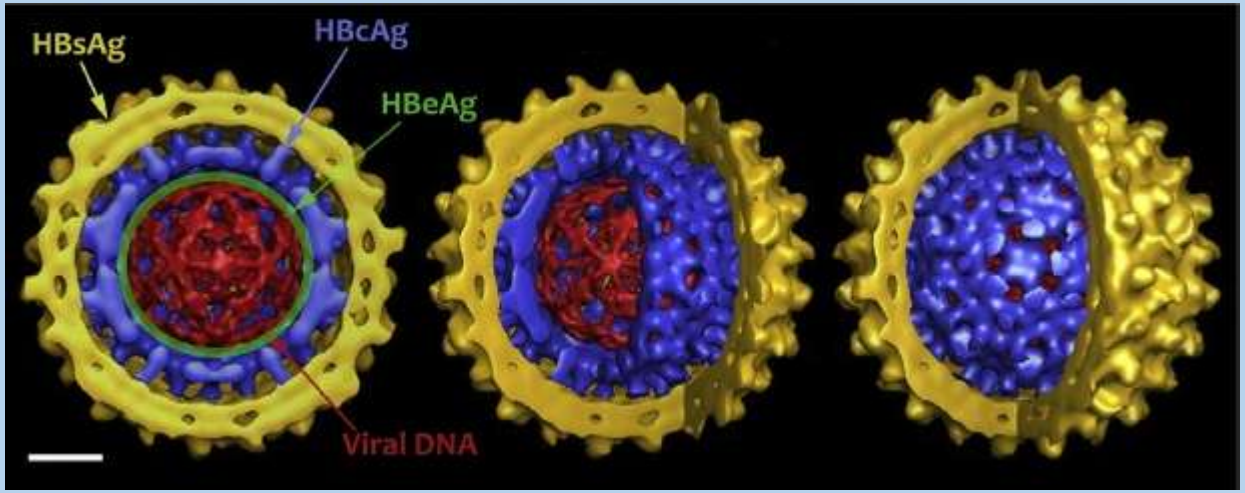
MAY 2006

- **1) Circulating immune complexes** involving viral antigens and host antiviral antibodies, and endogenous antigens modified by viral injury and host **autoantibodies.**
- **2) *In situ* immune-mediated mechanisms** involving viral antigens bound to glomerular structures.
- 3) A direct cytopathic effect of viral proteins on glomerular cells or Tubulointerstitial affection.
- **4) Hemodynamic disturbance,** hantavirus or severe acute respiratory syndrome coronavirus, (disseminated intravascular coagulopathy, and multiorgan failure).
- **5) Nephrotoxicity** of antiviral therapy (occasionally) .
- 6) Other: (HCV)-induced **production of circulating cryoglobulins** is induced as an abnormal host response to infection .

Viral Nephropathy

Acute glomerulonephritis	Chronic glomerulonephritis	Interstitial nephritis
• Parvovirus • Hepatitis • Measles • Yellow fever • Epstein–Barr virus	HBV HIV CMV Parvo B19	• Hantavirus • Severe acute respiratory syndrome coronavirus • Mumps • Dengue fever • Epstein–Barr virus • Influenza A • Coxsackie B virus • Cytomegalovirus (congenital)

1- HEPATITIS B VIRUS ASSOCIATED GLOMERULOPATHY



GLOMERULONEPHRITIS ASSOCIATED WITH HEPATITIS B VIRUS

- An estimated 350–400 million people worldwide are infected with HBV.
- The reported prevalence of HBV-associated nephropathy closely parallels the geographic patterns of prevalence of HBV.
- In endemic areas, transmission is usually vertical (from infected mother to child).
- Horizontal transmission occurs via direct contact with blood (e.g. blood transfusions) or mucous membranes (e.g. during sexual contact), or via the percutaneous route upon contact with blood or body fluids (e.g. during intravenous drug use and needle sharing).

Morphological forms

- **Membranous nephropathy:**
- **The most common HBV-associated nephropathy.**
- **Membranoproliferative glomerulonephritis:**
- **Deposition of immune complexes in the mesangium and subendothelial spaces.**
- **Mesangial proliferative glomerulonephritis:**
- **Glomerular deposition of immunoglobulin G (IgG), complement C3, and HBsAg has been reported.**
- **immunoglobulin A (IgA) nephropathy,**
- **Focal segmental glomerulosclerosis, and polyarteritis nodosa.**
- **A vasculitis affecting medium-sized arteries in most cases.**
    - J. Cai, Xet al., "*Clinical Journal of the American Society of Nephrology, 2012.*

Pathogenesis

- **Immune reactions :**
- **Glomerular deposition of immune complexes .**
- **HBV antigens (HBsAg) and hepatitis B core antigen (HBcAg) and HBeAg deposition .**
- **They can upregulate complement mediated inflammatory gene pathways and contribute to the pathogenesis of nephropathy .**

J. Ren et al., *Journal of Medical Virology,* 2006.

- **C. L. Deng, *World Journal of Gastroenterology,* 2006.**

- **Treatments used in chronic HBV may also be associated with renal abnormalities (hypophosphatemia, proximal tubulopathy,and renal acidosis) .**
- **Potential comorbidities encountered in HBV patients (diabetes mellitus, high blood pressure, and HIV or HCV coinfection).**

- H. Izzedine., et al.T*he American Journal of Kidney Diseases,* 2005.

Clinical characteristics

A) In children:

- There is a strong male preponderance.
- The most frequent presentation is nephrotic syndrome(64%), microscopic hematuria(57%), and normal or mildly impaired renal function.
- Pediatric chronic HBV carriers often do not have overt liver disease.
- **Membranous glomerulonephritis is most frequently reported .**

S. O. Ozdamar,e t al " *Pediatric Nephrology , 2003.*

B) In adults:

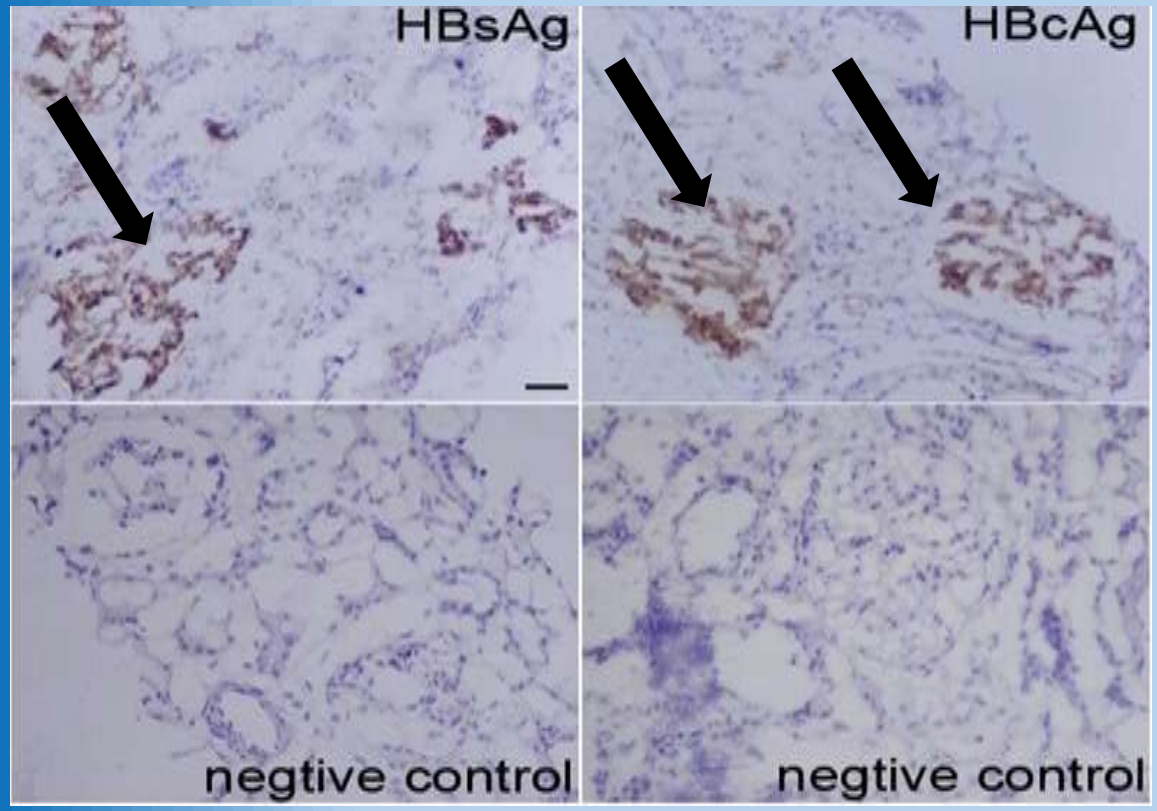
- Proteinuria or the nephrotic syndrome are the most common manifestations.
- **Adult male predominance is less obvious** than in pediatric populations.
- Adults are more likely than children to have hypertension, renal dysfunction, and clinical evidence of liver disease.
- **Mesangial proliferative forms with IgA deposits seem to be most common .**

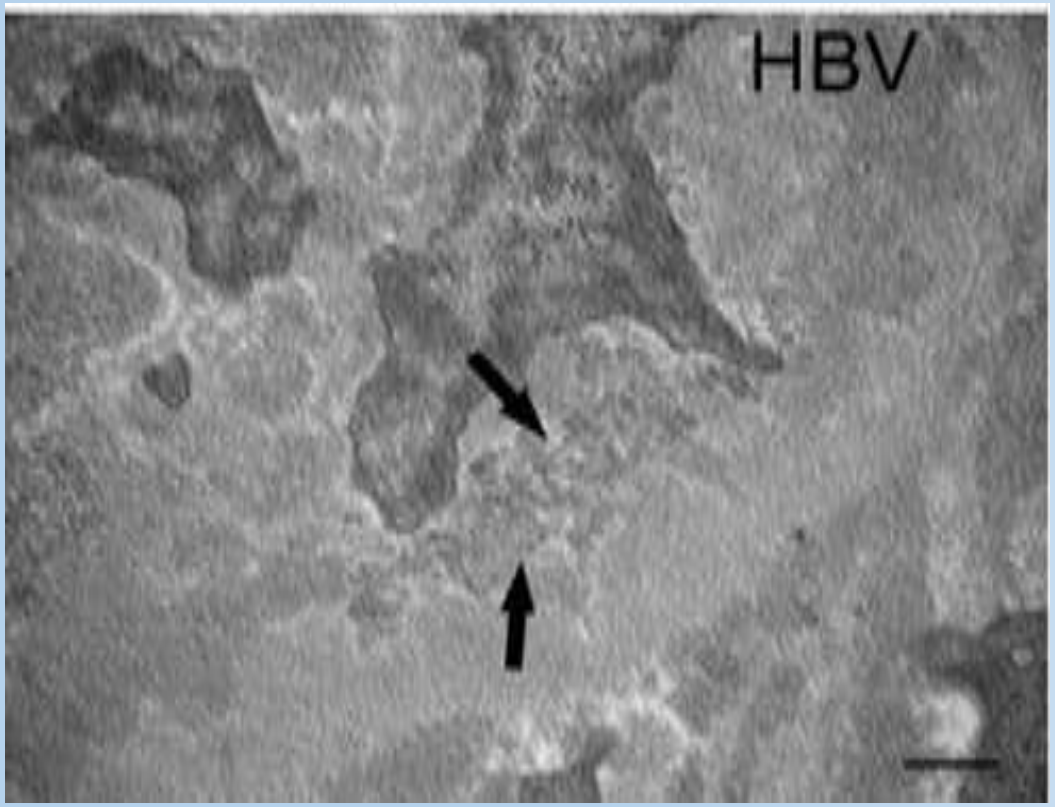
Z. Yi, et al *Annals of Hepatology,* 2011.

Diagnosis

- 1- Persistence of circulating HBV or HBV DNA, absence of other causative agents .
- 2- Detection of HBV-specific antigen(s) or viral genome in the glomerulus.
- 3- Laboratory testing:
- liver biochemistries (serum alanine aminotransferase, γ-glutamyltransferase, and bilirubin levels).
- HBeAg is present in 80% of patients, who might also have high titers of anti-hepatitis B core antigen.
- Serum C3 and C4 levels can be low in 20–50% of patients.

J.-J. Lee, .*The American Journal of Kidney Diseases, 2010.*





Detection of viral antigens and particles in renal tissues.

Immunohistochemical staining of frozen sections.

(b) Electron microscopy. The virus particles can be found in the base membrane of the glomerulus

Dan Kong .International Journal of Infectious Diseases 17 (2013) e535–e538

Prognosis

- **In children:**
- Favorable.
- Stable renal function and high rates of spontaneous remission have been reported .
- **Adults :**
- Typically develop progressive disease.
- Up to 29% of patients had progressive CKD and another 10% developed ESRD over 5 years require renal replacement therapy .

J. Cai, X. Fan, L. Mou et al. CJASN, *2012.*

- Poorer outcomes :
- Patients with nephrotic-range proteinuria and abnormal liver function tests at presentation.
- Vertical transmission is associated with than horizontal transmission.
- Endemic versus sporadic infection.

H. Izzedine, et al., *Kidney International 2004.*

Immunization

- **While awaiting an ideal agent for treatment of HBV-associated glomerulopathy, active immunization remains the most effective means of immunoprophylaxis.**

  - Poland GA and Jacobson (2004) *N Engl J Med* .

- **In Taiwan, active immunization of all newborns since 1984 has led to a dramatic (10-fold) decline in the incidence of neonatal HBV infection and its sequelae.**

  - Chang MH *et al. (1997) N Engl J Med*

- **In the US, universal vaccination of infants began in 1991, and a 67% reduction in HBV infection was recorded 10 years later.**

  - Duclos P (2003) *Expert Opin Drug Saf* .

Treatment

- Should ideally achieve the following objectives:
- (i) Amelioration of nephrotic syndrome and its complications.
- (ii) Preservation of renal function.
- (iii) Normalization of liver function and prevention of hepatic complications of HBV.
- (iv) Permanent eradication of HBV.

Anti-HBV Drugs and Renal Dysfunction

- ***Nucleotide Analogues:***
- ***A***ssociated with putative renal toxicity which is related to an accumulation of the nucleotides metabolites in renal tubular cells.
- **This toxicity is more frequent with cidofovir > adefovir > tenofovir.**
- ***Nucleoside Analogues:***
- ***Lamivudine:***
- Rare cases of lamivudine-induced tubular dysfunction have been reported .
- ***Entecavir:***
- Considered to be nonnephrotoxic.
- Rare cases of lactic acidosis have been reported .
- ***Telbivudine:***
- *A better renal safety of LDT, were confirmed in the prospective Phase III GLOBE trial, over 2 and 4 years of treatment .*
- *After 2 years of treatment, LDT showed a better efficacy as compared to LAM. At year 2, the eGFR in LDT-treated patients had increased from 94.9 mL/min/1.73m2 at baseline, to 112.3 mL/min/1.73m2 at week 104 ($P < 0.0001$).*

- ***Y.Wang, Set al., "Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B," Journal of Viral Hepatitis, vol. 20, no. 4, pp. e37–e46, 2013.***

Transplantation

- Transplanted patients most of the time require long-term immunosuppression to prevent graft rejection, which can in turn favour HBV reactivation.

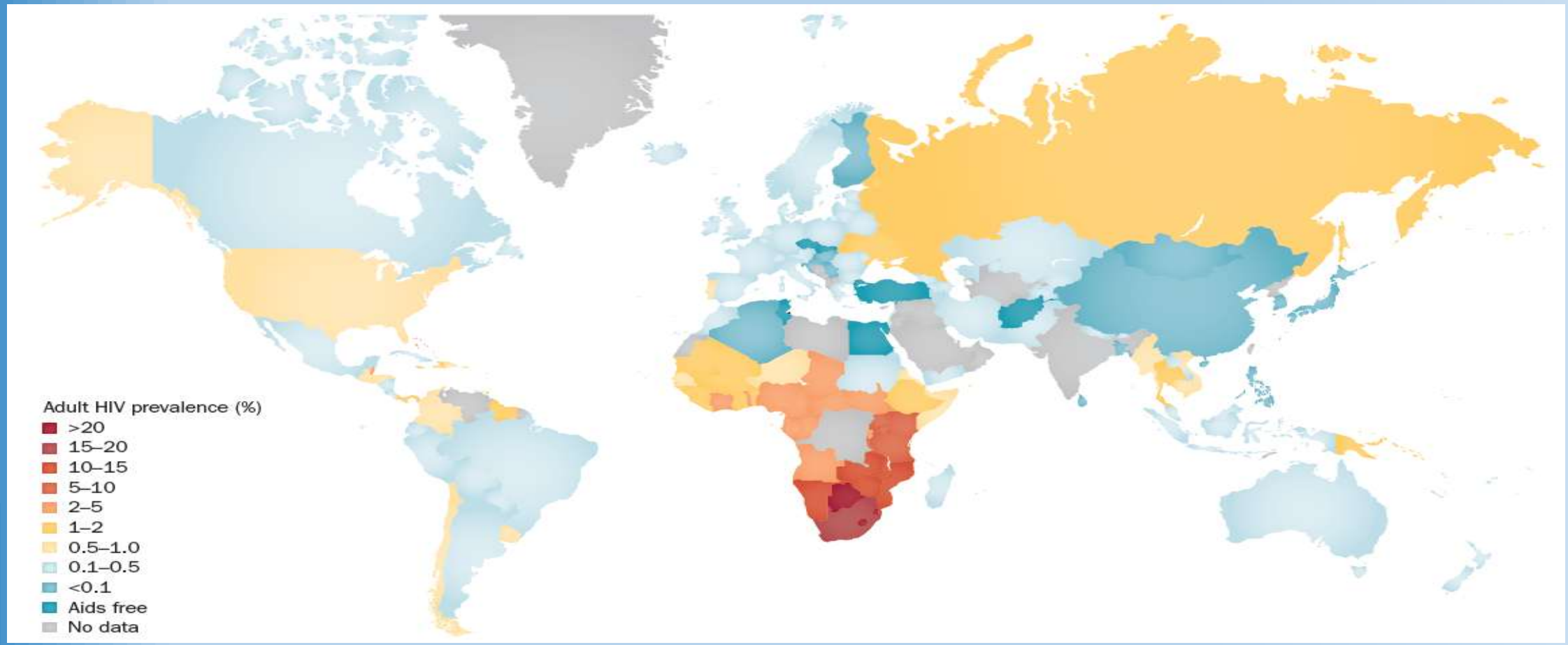
- Reactivation is characterised by an abrupt reappearance or rise in HBV DNA levels in the serum of patients with previously inactive or resolved HBV infection.

- HBV infection is associated with decreased survival after renal transplantation and amore frequent need for retransplantation .

Gilbert Deray., et al. Advances in Hepatology 2015

HIV-RELATED GLOMERULAR DISEASES

Prevalence of HIV infection in adults in 2009



(http://en.wikipedia.org/wiki/File:AIDS_and_HIV_prevalence_ 2009.svg)

Renal diseases in human immunodeficiency virus-infected patients

HIV-specific glomerular disease	
HIVAN	Detectable viral load, a high amount of proteinuria, albuminuria, RPGN
HIVIC	Proteinuria and/or hematuria, variable manifestation including AKI
TMA	AKI, proteinuria, hematuria with microangiopathic hemolytic anemia and thrombocytopenia

HIV-non-specific glomerular disease	
HCV-related MPGN/ cryoglobulinemia	Proteinuria and/or hematuria, nephritic syndrome, a decrease in serum complements
Diabetec nephropathy	Proteinuria (microalbuminuria to nephrotic syndrome), a decrease in GFR
Glomerular sclerosis	Older patients, hypertension, no or low amount of proteinuria, coexistence of atherosclerotic diseases
Membranous glomerulopathy	Nephrotic syndrome; idiopathic and secondary causes associated with HBV or cancers
Minimal change disease	Nephrotic syndrome, use of NSAIDs
IgA nephropathy	Hematuria and/or proteinuria with or without renal failure
Post-infectious glomerulonephritis	Hematuria and/or proteinuria with or without renal failure
ART-associated tubular injury	
Acute tubular necrosis	Use of TDF
Cristal nephropathy	Use of IDV and ATV
Acute or chronic interstitial nephritis	Use of ATV

ART: Antiretroviral therapy; TDF: Tenofovir disoproxil fumarate; IDV: Indinavir; ATV: Atazanavir.

Minoru Ando, Naoki Yanagisawa ., World J Nephrol 2015

Traditional and human immunodeficiency virus related factors associated with chronic kidney disease

- Black race
- Older age
- Low CD4 cell count
- High HIV-RNA viral load
- Diabetes mellitus
- Hypertension
- Hepatitis C virus coinfection
- Proteinuria
- Albuminuria
- eGFR < 90 mL/min per 1.73 m2
- Elevation of urinary tubular markers
- Use of TDF or ATV

Ando M et al . Chronic kidney disease in HIV . *World J Nephrol* 2015

TDF: Tenofovir disoproxil fumarate; ATV: Atazanavir.

Renal effects of cART

Class	Drug	Renal abnormality
Nucleoside reverse transcriptase inhibitors	Abacavir	AIN (case report) Fanconi syndrome (case report)
	Didanosine	Fanconi syndrome AKI Lactic acidosis Nephrogenic diabetes insipidus (case reports)
	Lamivudine	Renal tubular acidosis Hypophosphataemia (case report)
	Stavudine	Renal tubular acidosis Hypophosphataemia (case report)
	Zidovudine	None reported
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	None reported
	Delavirdine	None reported
	Efavirenz	Nephrolithiasis
Nucleotide reverse transcriptase inhibitors	Tenofovir	Proximal tubular dysfunction with Fanconi syndrome Nephrogenic diabetes insipidus AKI CKD
Protease inhibitors	Amprenavir	None reported
	Atazanavir	AIN (case report)
	Darunavir	None reported
	Fosamprenavir	None reported
	Indinavir	AKI (AIN) CKD (AIN) Nephrolithiasis Intratubular drug precipitation Papillary necrosis Hypertension Renal atrophy
	Lopinavir	None reported
	Nelfinavir	Nephrolithiasis (case report)
	Ritonavir	AKI
	Saquinavir	AKI in association with Ritonavir
	Tipranavir	None reported
Fusion or entry inhibitors	Enfuvirtide	Membranoproliferative glomerulonephritis (case report)
	Maraviroc	None reported
Integrase inhibitor	Raltegravir	None reported

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; CKD, chronic kidney disease.

Pathology

- **1-Classical HIV-associated nephropathy (HIVAN):**
- Histological features of FSGS with tuft collapse or, more rarely, mesangial hyperplasia.
- A direct effect of HIV or viral proteins on renal epithelium.

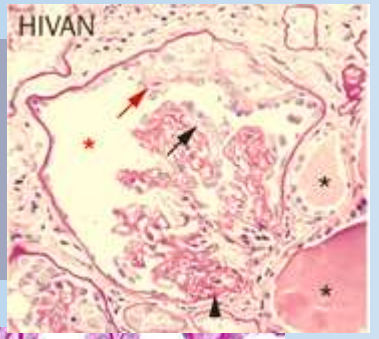
Simard, M. C. et al. *J. Virol.* 76, 3981–3995 (2002).

- **2- HIVIC OR lupus like glomerulonephritis :**
- Predominantly mesangial immune deposits.
- This group also includes other immune-complex-mediated glomerulonephritides with more-heterogeneous histological features.
- **3- Immunotactoid glomerulonephritis :**
- The true role of HIV infection in glomerulopathies of this type is also uncertain.
- **4- HIV-associated thrombotic microangiopathy/hemolytic uremic syndrome :**
- HIV is the main, but not sole, etiological factor.

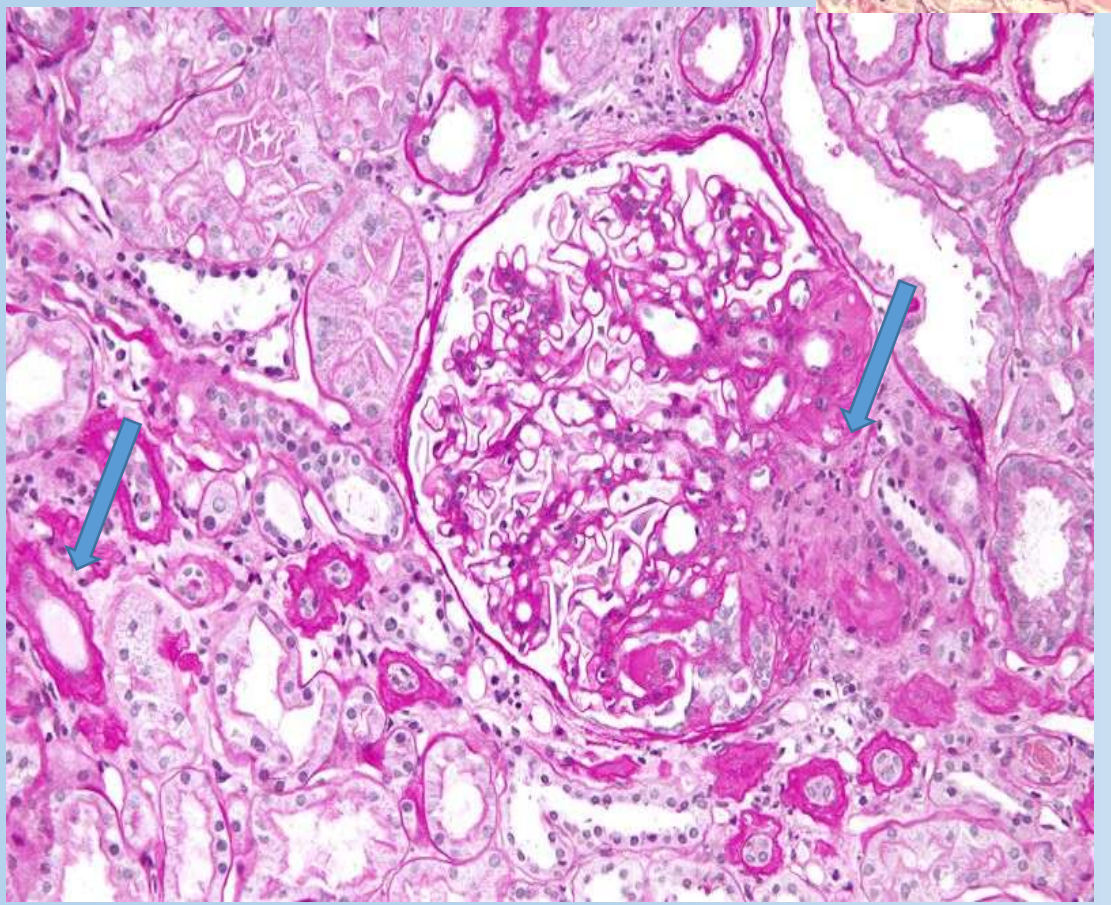
Ethnic/geographic background is an important determinant of the type of glomerulopathy associated with HIV (collapsing FSGS is prevalent in patients of African descent).

- Zuo, Y. *et al. J. Am. Soc. Nephrol. 17, 2832–2843 (2006).*

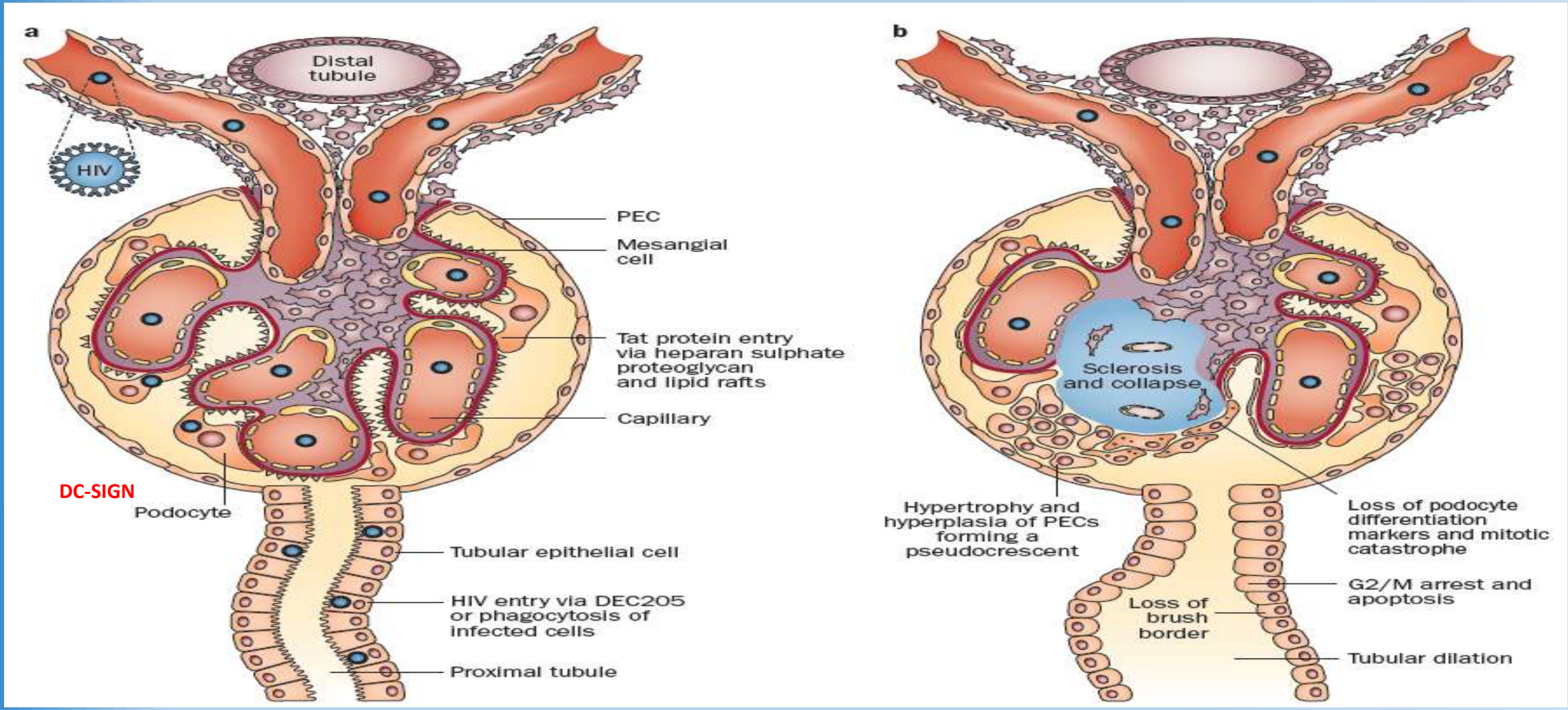
HIVAN

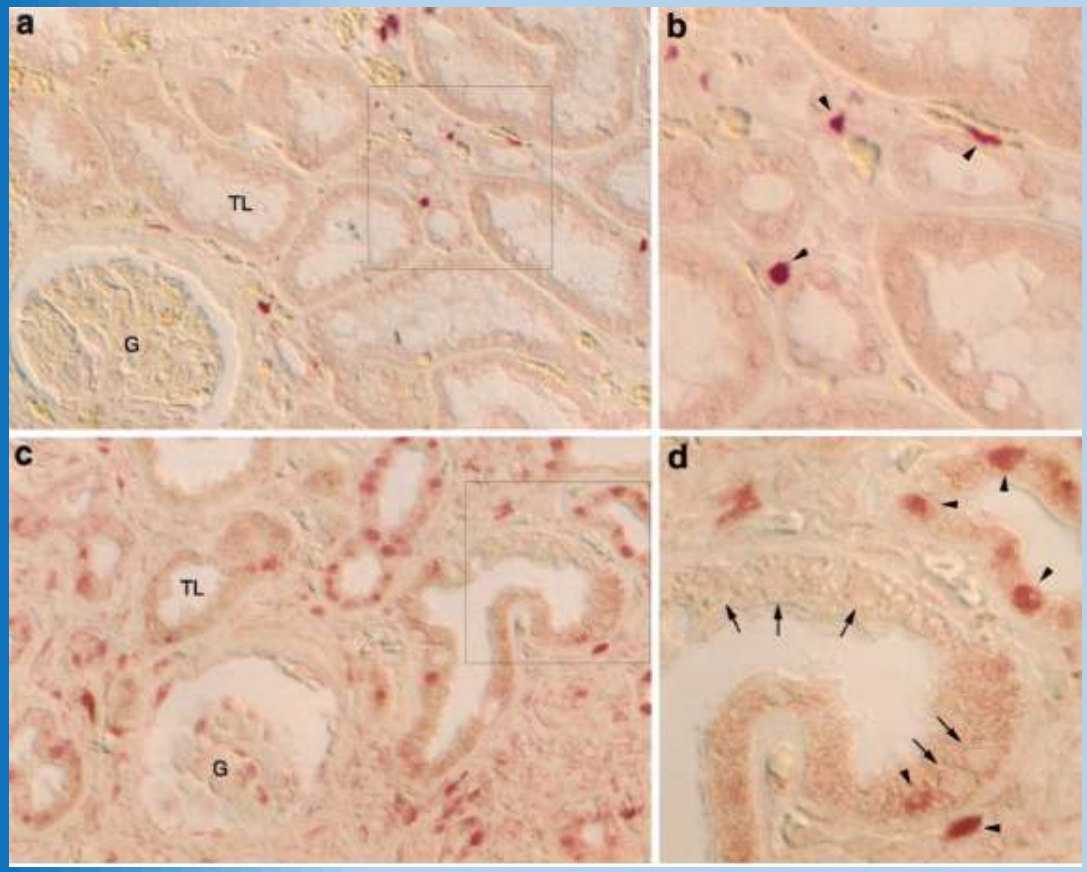


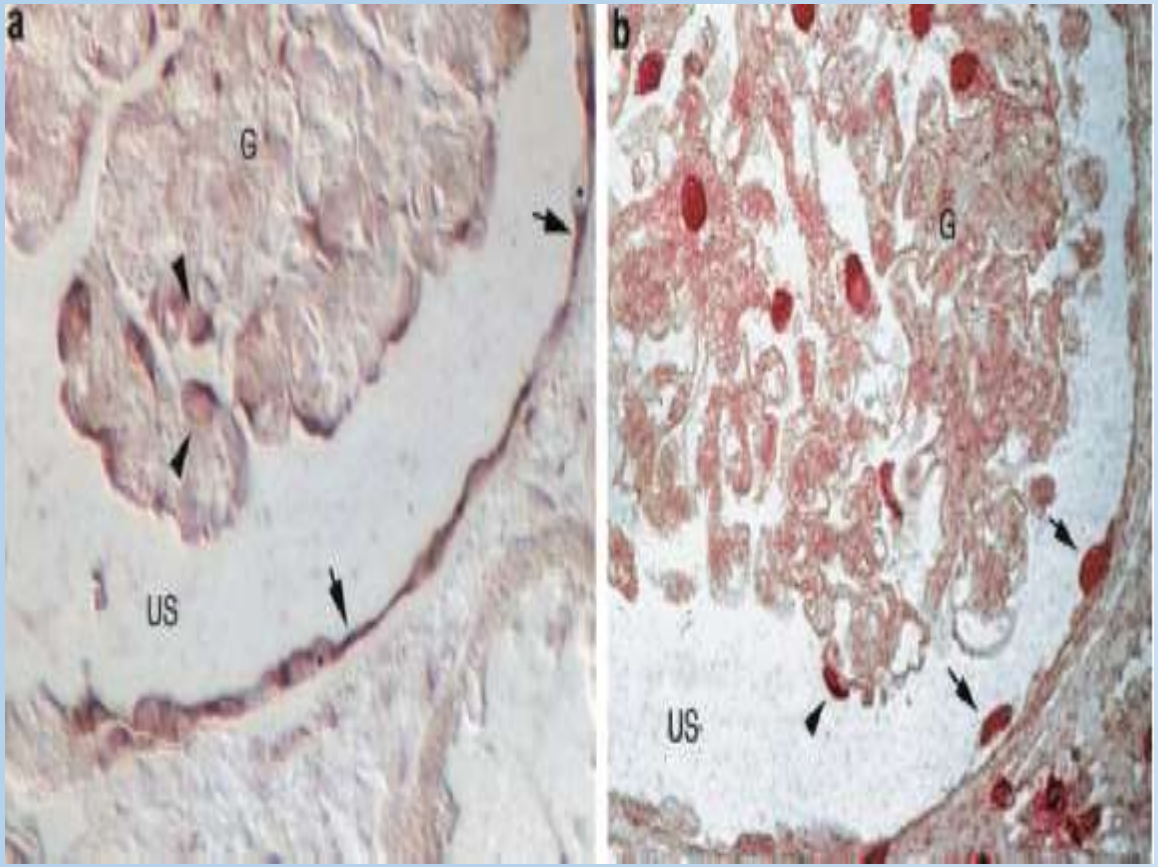
- The FSGS variant of HIVAN is the most commonly reported pathology
- affects up to 10% of HIV-infected patients of African descent—mainly males .
- Glomerular changes associated with this variant are capillary wall collapse of varying severity, with widening of Bowman's space.
- Tubular cells might undergo degenerative changes, necrosis or flattening.
- Large dense casts can develop in dilated tubules.



Mechanisms of collapsing glomerulopathy in HIVAN







- DNA *in situ PCR for HIV-1 proviral DNA. (a) In situ PCR on seropositive patient who had no renal disease. Positive amplification* signal for viral DNA is seen as red staining

Clinical characteristics

- Nephrotic-range proteinuria and renal insufficiency.
- Hypertension and edema are uncommon.
- In overt cases, ultrasonography typically reveals enlarged, highly echogenic kidneys, which probably develop in response to microcystic tubular dilatation.
- Before effective antiretroviral treatment was available, clinical progression was rapid.
- Intensive antiretroviral treatment delays progression.

Xie, X. *et al. J. Am. Soc. Nephrol. 25,1800–1813 (2014).*

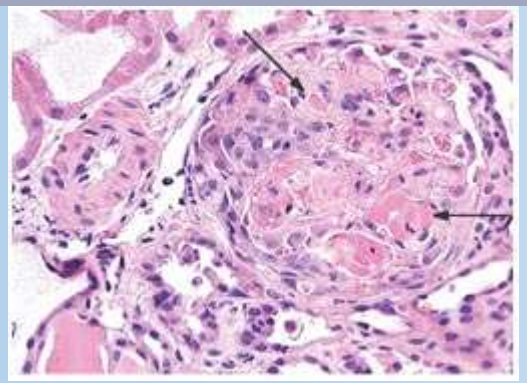
HIVIC

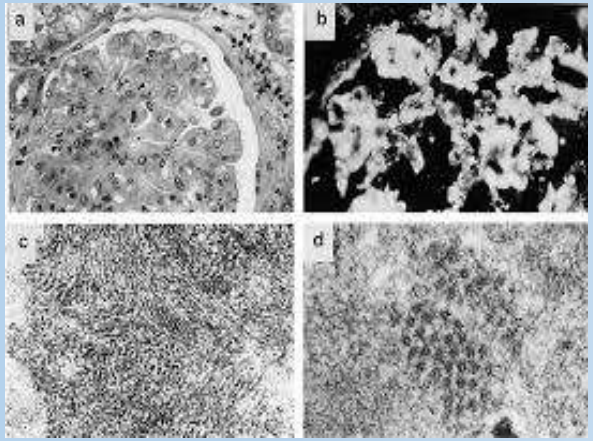
- Pathology of the HIV-associated disease mediated by immune complexes resembles lupus nephropathy.
- The clinical presentation is nephrotic syndrome with microscopic hematuria.
- Progression to renal failure occurs, but more slowly than in HIVAN.
- Viral antigen has been detected in glomeruli, and antibodies eluted from the kidney react with HIV antigens in circulating immune complexes (IgA-p24 antigen, IgG-p24 and IgG-gp120).

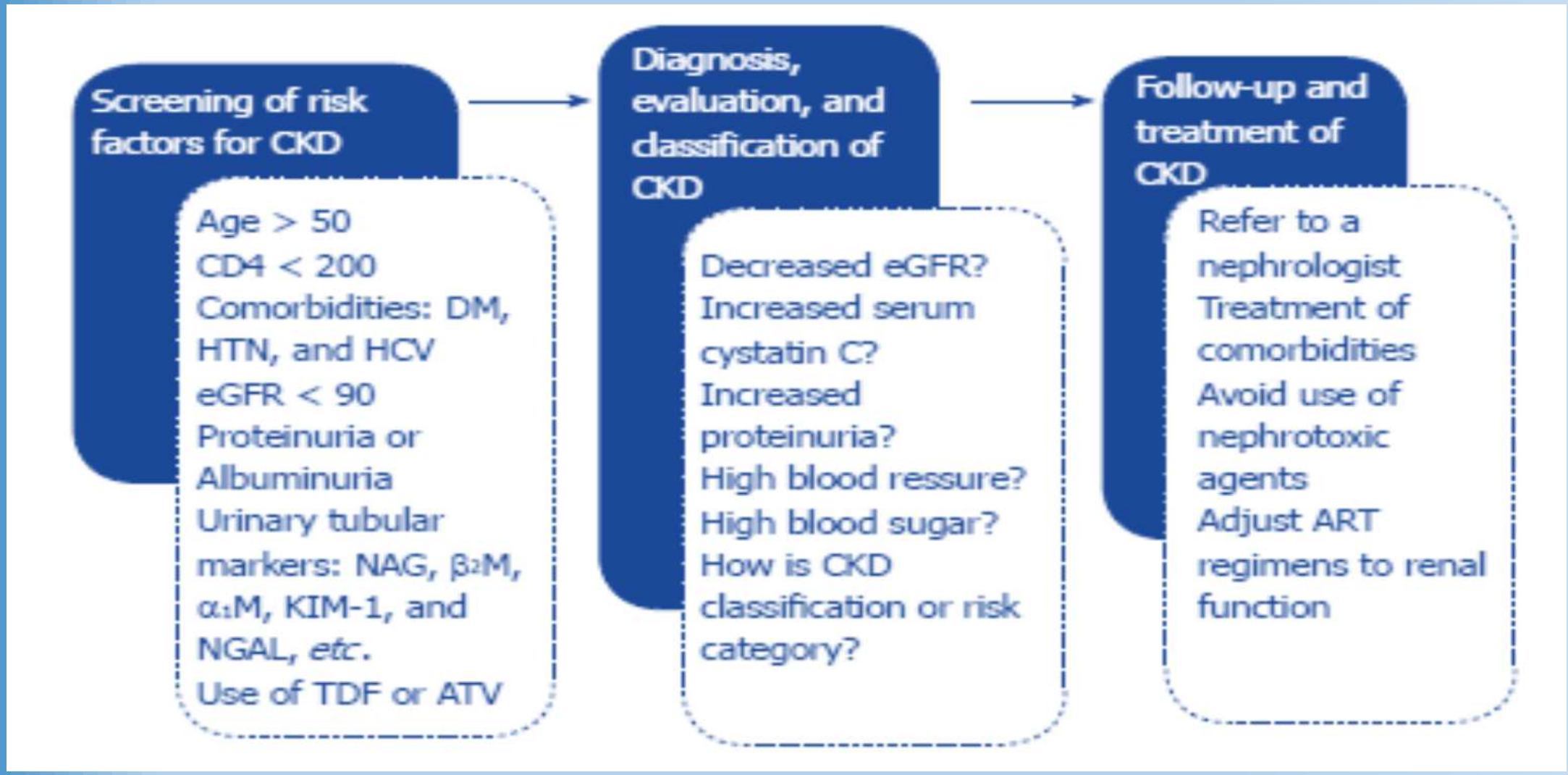
Khatua, A. K., Virology 408, 119–127 (2010).

Thrombotic microangiopathy/hemolytic uremic

- Present with acute renal failure, microscopic hematuria, and non-nephrotic proteinuria.
- Multiorgan involvement is frequent and prognosis is poor, with a high rate of mortality.
- Multifactorial etiologies encompass drugs, neoplasia, lymphoma and infection.







Flow chart for management of chronic kidney disease in human immunodeficiency virus-infected patients.

Minoru Ando, Naoki Yanagisawa World J Nephrol 2015 July 6; 4(3): 388-395

Therapy
Antiretroviral therapy

- **Current guidelines, therefore, recommend HIVAN as an indication for initiation of cART irrespective of CD4+ lymphocyte count.**

Lucas, G. M. et al. Clin. Infect. Dis. 59, e96–e138 (2014).

- **Decline in the incidence of HIVAN and HIV-associated ESRD in the USA after the introduction of cART, suggest that effective control of viral replication can prevent the development of HIVAN.**
- **The DART study conducted in Uganda and Zimbabwe, showed improvement in GFR by 1.9–6.0 ml/min/1.73 m2 after 4–5 years of cART .**

Stohr, W. et al. Antivir. Ther. 16, 1011–1020 (2011).

Outcome and Prognosis Factors in HIV-Infected Hemodialysis Patients

Jérôme Tourret,* Isabelle Tostivint,* Sophie Tézenas du Montcel,† Jennifer Bragg-Gresham,‡ Svétlana Karie,* Cécile Vigneau,§ Jean-Baptiste Guiard-Schmid,‖ Gilbert Deray,* and Corinne Isnard Bagnis*

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HIV-infected patients who are on hemodialysis have a worse prognosis than noninfected patients who are on hemodialysis. Their outcome in the highly active antiretroviral therapy (HAART) era remains unclear. Outcomes in patients who were enrolled in the French Dialysis in HIV/AIDS (DIVA) cohort were determined in a 2-yr prospective follow-up. All HIV-infected patients who were on hemodialysis in France on January 1, 2002, were included and followed prospectively until January 1, 2004. Patients' survival was examined by Kaplan-Meier method, and mortality risk factors were examined using uni- and multicovariate analyses. Survival was compared with that of 584 hemodialysis patients who did not have HIV or diabetes and were enrolled in the French Dialysis Outcomes and Practice Patterns Study II (DOPPS II) in the same period (after standardization for the average age, gender, and ethnicity of the DIVA cohort). A total of 27,577 patients were receiving hemodialysis in France at the beginning of the study; 164 (0.59%) were infected with HIV, 72% were male, mean age was 44.8 ± 10.9 yr, and 65% were black. The 2-yr survival rate was 89 ± 2% and statistically indistinguishable from the survival of the French cohort extracted from the DOPPS II study. Significant mortality risk factors were low CD4 cell count (hazard ratio [HR] 1.4/100 CD4 cells per mm^3 lower), high viral load (HR 2.5/1 Log per ml), absence of HAART (HR 2.7), and a history of opportunistic infection (HR 3.7), the last two being independent (HR 2.6 and 3.6, respectively). Survival of HIV-infected patients who are hemodialysis has greatly improved. A prospective cohort of paired hemodialysis patients with and without HIV is required to compare better their mortality in the HAART era.

Clin J Am Soc Nephrol 1: 1241–1247, 2006. doi: 10.2215/CJN.02211205

Table 2 – Selection criteria in HIV-positive patients for kidney transplantation

- CD4+ lymphocyte count > 200 cells/mm3 for at least 6 months
- Undetectable viral load (< 50 RNA copies/mL) for at least 6 months
- Treatment using HAART for at least 6 months
- No AIDS-defining diseases following HAART start

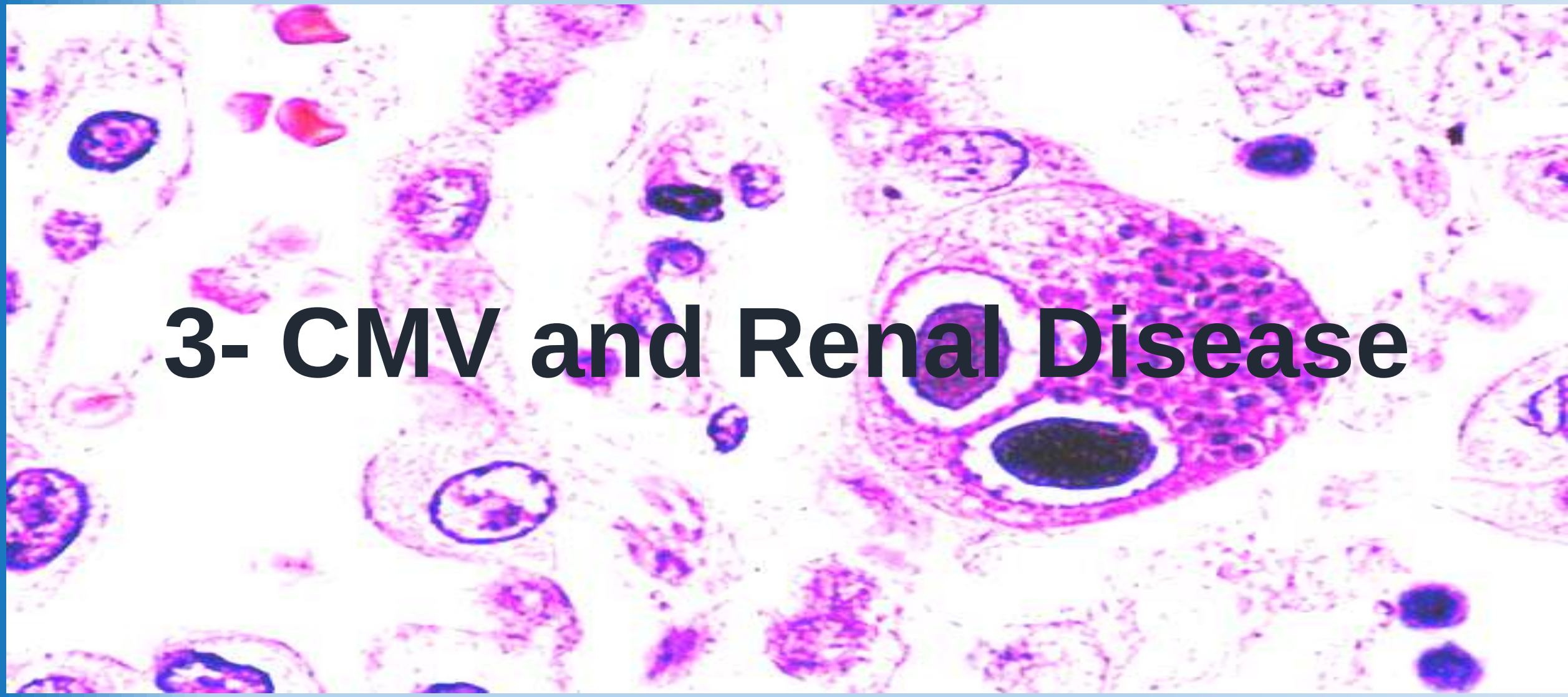
Roland ME, Stock PG. Review of solid-organ transplatation HIV-infected patients. Transplantation 2003; 75:425-9.

Table 1 – Patient and kidney graft survival in positive-HIV patients undergoing kidney transplantation

Authors	n	Follow-up time (months)	Patient survival	Graft survival
		before HAART		
Tzakis *et al.*[10] (1990)	5	36	80%	80%
Erice *et al.*[9] (1991)	11	30	64%	54%
Swanson *et al.*[11] (USRDS data) (2002)	32	60	71%	44%
		after HAART		
Stock *et al.*[13] (2003)	10	16	100%	100%
Roland *et al.*[14] (2003)	29	10	92%	85%
Abbott *et al.*[15] (USRDS data) (2004)	47	36	95%	97.3%
Kumar *et al.*[2] (2005)	40	24	82%	71%
Qiu *et al.*[16] (UNOS data) (2006)	38	60	91.3%	76.1%
Roland *et al.*[19] (2008)	18	36	94%	83%
Gruber *et al.*[18] (2008)	8	15	100%	88%
Locke *et al.*[17] (UNOS data) (2009)	100	12	95.4%	87.9%

USRDS, United States Renal Data System; UNOS, United Network for Organ Sharing.

Roland ME, Stock PG. Review of solid-organ transplatation HIV-infected patients. Transplantation 2013.



3- CMV and Renal Disease

- The first exposure to CMV occurs during the first two decades of life.
- The main host defense against CMV is cell-mediated immunity; however, virus-specific antibodies may also modify the disease caused by this virus.
- Following primary infection, CMV is maintained in a latent state by integration within the host cell controlled by a well functioning immune system.
- Any dysfunction of the immune system will allow for increased levels of CMV replication.
- Cytomegalovirus (CMV) is the most frequent opportunistic infection after renal transplantation .

Preiksaitis JK, . et al.American Journal of Transplantation 2015.

Razonable RR,et al. J Clin Microbiol 2012.

Transmission

- Saliva .
- Sexual contact .
- Placental transfer .
- breast-feeding .
- Blood transfusion .
- Solid organ transplantation (SOT).
- Hematopoietic stem cell transplantation .

Crough T and Khanna R. Clinical Microbiology Reviews 2009; 22 (1): 76-98.

Risk Category	Donor (D) or Recipient (R) Seropositivity (+/-)
High	D+/R-
Intermediate*	D+/R+, D-/R+
Low	D-/R-

* D+/R+ generally at higher risk than D-/R+

Fishman JA, Emery V, Freeman R, et al. Cytomegalovirus in transplantation – challenging the status quo. *Clinical Transplantation*. 2007;21:149-158.

CMV in Solid Organ Transplantation

- CMV was first isolated in a renal transplant recipient in 1965 .
- More than 50% of solid organ transplant recipients show evidence of CMV infection, with 10 to 50% of patients developing symptomatic disease, depending on the serostatus of the recipient.
- In an immunocompetent host, primary CMV infection often is asymptomatic, although it can manifest as a mononucleosis-like syndrome.
- In an immunocompromised hosts, primary CMV infection, reactivation of latent infection, or reinfection with a different strain usually causes CMV disease .

- **Rubin RH. Current Opinion in Infectious Diseases 2007; 20 (4): 399-407.**

VARIABLE FORMS OF INFECTION

- **1. *Primary CMV disease* : an allograft (or a transfusion product) is obtained from a seropositive donor and is transplanted into a seronegative recipient.**

If no antiviral protocol utilized, approximately 60% of these D+/R- patients will become clinically ill, usually at around 4 weeks posttransplant.

- **2. Reactivation disease: This occurs when a seropositive individual reactivates endogenous virus which then has the potential for producing clinical disease.**
- **3. Superinfection: This occurs when an allograft from a seropositive donor is transplanted into a seropositive recipient and the virus that is reactivated is of donor origin .**

Rubin RH. Current Opinion in Infectious Diseases 2007; 20 (4): 399-407.

OTHER EFFECTS OF CYTOMEGALOVIRUS IN TRANSPLANT RECIPIENTS

- Suppresses host defenses, predisposing to secondary invasion by such pathogens as Pneumocystis jiroveci, Candida, and Aspergillus species,…..

  - Reinke P, et al. Transplant Infectious Disease 2009

- Contributes to the risk of EBV-mediated posttransplant lymphoproliferative disorder (PTLD) , and increased risk of graft rejection .

- The mechanisms for these effects include altered T cell subsets and synthesis and display of major histocompatibility antigens, and elaboration of the array of proinflammatory cytokines, chemokines, and growth factors.

Pescovitz MD. Transplantation 2006

DIAGNOSIS

➢ **Serology:**

- **Has no role in the diagnosis of active CMV disease posttransplantation .**

➢ **Antigenemia :**

- **Directly immunostaining polymorphonuclear leukocytes (PMN) from blood specimens with monoclonal antibodies directed against the CMV lower-matrix protein (pp65) .**

➢ **Quantitative nucleic acid testing (QNAT) or polymerase chain reaction (PCR) :**

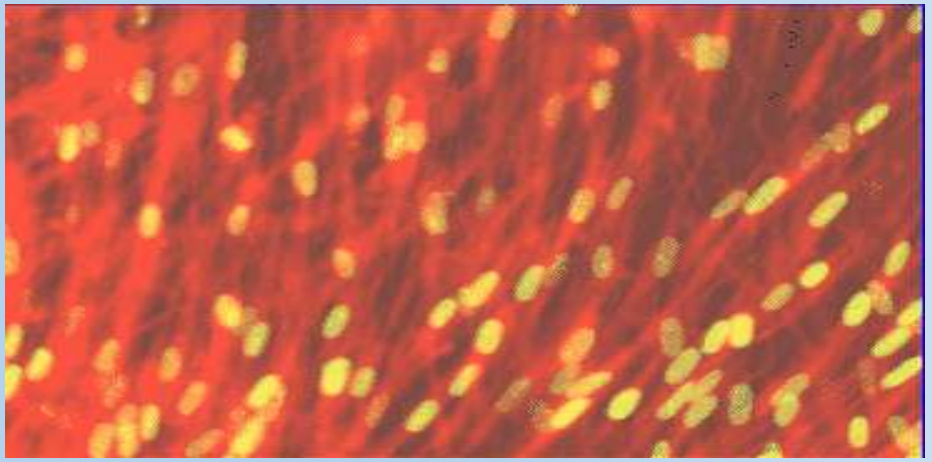
- Higher sensitivity and similar specificity than the pp65 antigenemia assay.
- The precision of QNAT viral load tests are such that changes in values should be at least 3-fold (0.5 log10 copies/mL) to represent biologically important changes in viral replication .

Kotton CN. American Journal of Transplantation 2013; 13 (s3): 24-40.

DIAGNOSIS

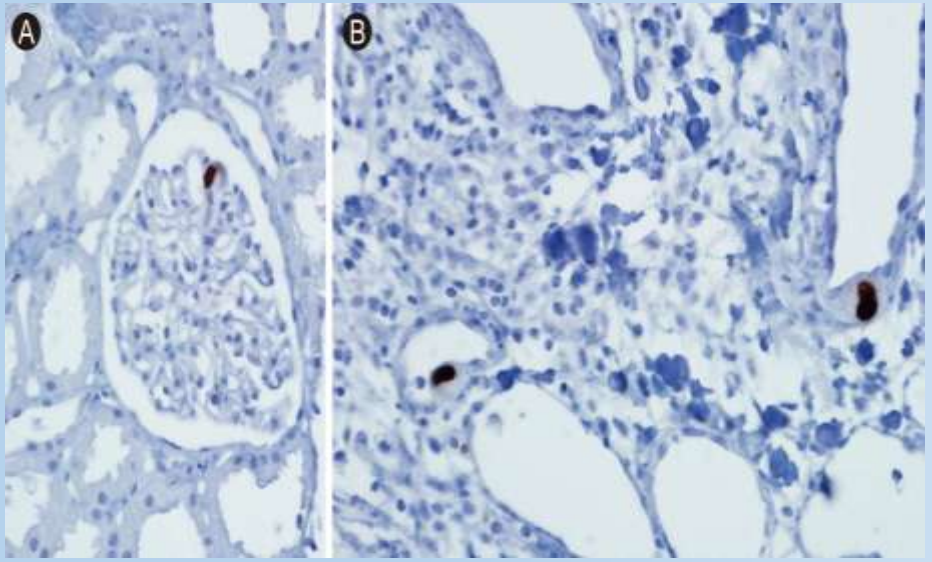
➢Viral cultures:

- Recovery of replicating CMV by cell culture (conventional tube and shell vial assay) has traditionally been the standard method for the diagnosis of CMV infection .
- Viral culture of blood for CMV has limited clinical utility .

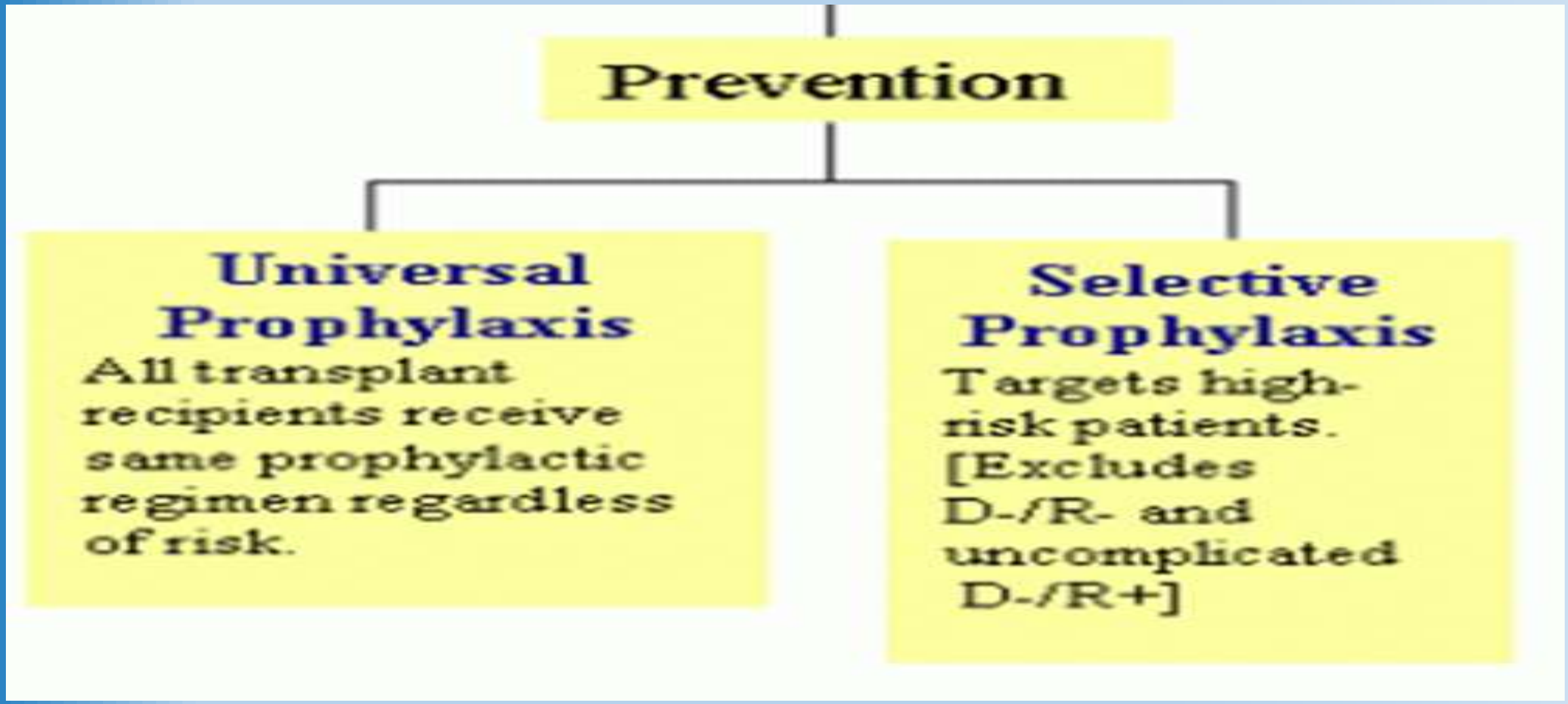


➢Histopathologic examination :

- The use of immunohistochemistry and/or in situ hybridization to identify CMV-infected cells .



Preiksaitis JK, J et al. American Journal of Transplantation 2005; 5 (2): 218-27.


Prevention
Universal Prophylaxis
All transplant recipients receive same prophylactic regimen regardless of risk.
Selective Prophylaxis
Targets high-risk patients. [Excludes D-/R- and uncomplicated D-/R+]

Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial

Paul D Griffiths, Anna Stanton, Erin McCarrell, Colette Smith, Mohamed Osman, Mark Harber, Andrew Davenport, Gareth Jones, David C Wheeler, James O'Beirne, Douglas Thorburn, David Patch, Claire E Atkinson, Sylvie Pichon, Paul Sweny, Marisa Lanzman, Elizabeth Woodford

Phase 2 trial
67 Patients Received Vaccine- 73 placebo
Antibody Titer increased in Vaccinated versus placebo group

Those who developed viremia after Tx , vaccinated patients had shorter viremia duration and numbers of days treatment

Lancet 2011; 377: 1256–

See Comment page 1

Centre for Virol
(Prof P D Griffiths
A Stanton RN, E McCarrell M
M Osman P
Prof V C Emery P
R S B Milne P
C E Atkinson M
E Rothwell RGN, N Old
T Haque FRCP
S Atabani MRCP
S Luck MBChB, S Prideaux BSc
Centre for Nephrology
(M Harber FRCP,
A Davenport FRCP, G Jones MRCP,
D C Wheeler FRCP, P Sweny FRCP,
R Khaanjul RN), Sheila Sherlock
Liver Centre and University
Department of Surgery, Royal
Free NHS Trust (J O'Beirne MRCP,
D Thorburn FRCP, D Patch FRCP,
Prof A K Burroughs FRCP),
Department of Infection &
Population Health, UCL Medical
School, London (C Smith PhD),
Pharmacy Department, Royal
Free NHS Trust, London
(M Lanzman MRPharmS,
E Woodford); and Clinical
Development, Sanofi Pasteur,
Marcy l'Etoile, France
(S Pichon MSc)

3000 cytomegalovirus genomes per mL received ganciclovir until two consecutive undetectable cytomegalovirus DNA measurements. Safety and immunogenicity were coprimary endpoints and were assessed by intention to treat in patients who received at least one dose of vaccine or placebo. This trial is registered with ClinicalTrials.gov, NCT00299260.

Findings 67 patients received vaccine and 73 placebo, all of whom were evaluable. Glycoprotein-B antibody titres were significantly increased in both seronegative (geometric mean titre 12 537 (95% CI 6593–23 840) versus 86 (63–118) in recipients of placebo recipients; p<0·0001) and seropositive (118 395; 64 503–217 272) versus 24 682 (17 909–34 017); p<0·0001) recipients of vaccine. In those who developed viraemia after transplantation, glycoprotein-B antibody titres correlated inversely with duration of viraemia (p=0·0022). In the seronegative patients with seropositive donors, the duration of viraemia (p=0·0480) and number of days of ganciclovir treatment (p=0·0287) were reduced in vaccine recipients.

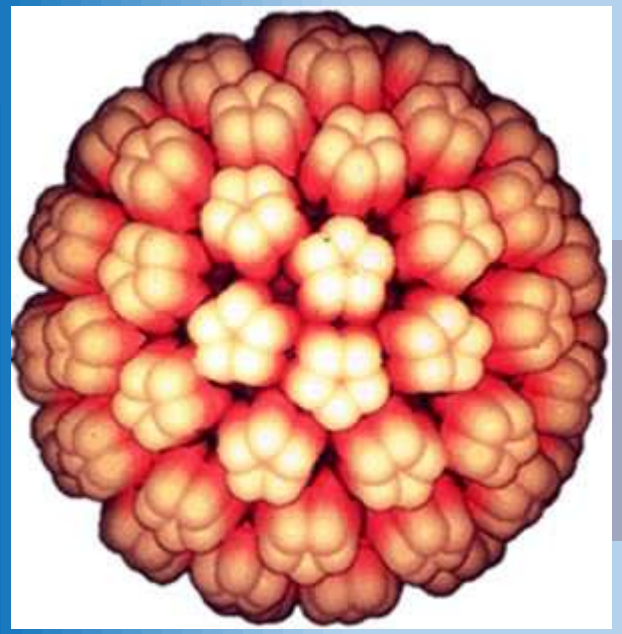
Interpretation Although cytomegalovirus disease occurs in the context of suppressed cell-mediated immunity post-transplantation, humoral immunity has a role in reduction of cytomegalovirus viraemia. Vaccines containing cytomegalovirus glycoprotein B merit further assessment in transplant recipients.

CYTOMEGALOVIRUS TREATMENT

- 1- Intravenous ganciclovir (5 mg/kg two times a day).
- 2-Oral valganciclovir (900 mg two times a day) .
- Dose reduction of the immunosuppressive therapy should be individualized
- The long-term follow-up revealed comparable treatment success rates, CMV recurrence rates and a low incidence of ganciclovir resistance .

Asberg A, et al. American Journal of Transplantation 2009; 9 (5): 1205-13.

- Until the following criteria are met:
- a. Clinical resolution of symptoms .
- b. Virologic clearance below the threshold negative value (test specific) monitor patients with viral load or pp65 antigenemia once a week .
- c. Minimum 2 weeks of treatment .



4-BK Virus Infection

- BK is a circular, double-stranded DNA virus from the polyomavirus family, which includes JC virus and SV40.
- Based on DNA sequence variations, BK can be divided into six subtypes or genotypes.
- Genotype I is the most frequent worldwide (80%), followed by genotype IV (15%).

Takasaka T, et al. J Gen Virol 2004; 85: 2821–2827

- First isolated from the urine of a renal transplant recipient with ureteric stenosis in 1971 .

Gardner SD, et al. Lancet 1971; 1: 1253–1257

- 20 years later was recognized as a cause of interstitial nephritis and allograft imapairment in renal transplant recipients

Purighalla R, et al. Am J Kidney Dis 1995; 26: 671–673.

Primary infection

- is often subclinical or manifests as a mild respiratory illness and is acquired in childhood.
- After primary infection, the virus establishes latency in the uroepithelium and renal tubular epithelial cells.
- In the setting of immunosuppression, the virus reactivates and begins to replicate, triggering a cascade of events starting with tubular cell lysis and viruria.
- The BK virus then multiplies in the interstitium and crosses into the peritubular capillaries, causing viremia and eventually invading the allograft, leading to various tubulointerstitial lesions and BKVN.
- Approximately one-third of patients with viruria will develop BK viremia (BKV) and, without intervention, could progress to BKVN (rates ranging from 1 to 10%).

Deirdre Sawinski and Simin Goral .Nephrol Dial Transplant (2015) 30: 209–217

RISK FACTORS

- **Immunosuppression**
- Induction : Rabbit anti-thymocyte globulin
- Maintenance tacrolimus- or mycophenolate mofetil (MMF)-based immunosuppression.
- Patients treated by cyclosporine had a lower rate of BKV at 6 and 12 months posttransplant, compared with the tacrolimus group.
- High-titer BKV (>4 log) .
- Absence of the HLA C7 allele in the donor or recipient increased the risk for sustained BKV in the recipient at least 3-fold.
- Hirsch HH, et al. Am J Transplant 2013; 13: 136–145

Donor risk factors	BK virus seropositive donor [22]
	Degree of HLA mismatching [21]
	HLA C7 [22]
Recipient risk factors	Older recipient age [21]
	Male recipient [21]
	Recipient race (non-African American) [21]
	Diabetes [21]
Transplant risk factors	Acute rejection episodes [8]
	Cold ischemia time [21]
	Delayed graft function [21]
	Ureteral stent placement [9,23,24]
	Anti-thymocyte globulin induction [25]
	Tacrolimus and/or MMF-based maintenance immunosuppression [14]

Nephrol Dial Transplant (2015) 30: 209–217
doi: 10.1093/ndt/gfu023
Advance Access publication 25 February 2014

BK virus infection: an update on diagnosis and treatment

Deirdre Sawinski and Simin Goral

Pre Tx Screen Or Not to Screen ?

- Screening of donors and recipients for BK seropositivity is neither mandatory nor routinely performed.
- Pretransplant BK antibodies are not clearly protective.

Hirsch HH, et al. N Engl J Med 2002; 347: 488–496

- However, there is growing evidence to suggest that the donor kidney may be the source of posttransplant BKV and BKVN , and that pretransplant screening of donors could identify which recipients are at greatest risk of developing BK.
- Patients who received a kidney from a BK-seropositive donor were more likely to develop BK infection (46%), compared with those whose kidney came from a seronegative donor (15%).

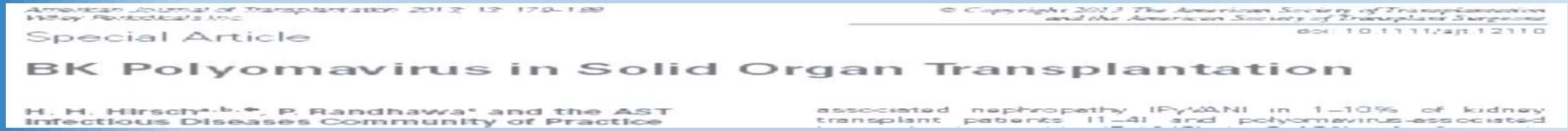
Bohl DL, et al. J Clin Virol 2008; 43: 184–189

SCREENING

- The incidence of viremia and viruria peaked at Month 3 with 28 and 31%, respectively, of patients testing positive.
- Incidence of BK peaked a second time at 12 months posttransplant.
- New onset BKV after 24 months posttransplant is rare .

Trofe-Clark J, et al. AJT , 2013

- Earlier (starting at 1 month posttransplant) and more frequent screening (monthly plasma screening for the first 6 months, then every 3 months until 2 years posttransplant) .



American Journal of Transplantation 2013; 13: 179–188
Wiley Periodicals Inc.

doi: 10.1111/ajt.12110

Special Article

BK Polyomavirus in Solid Organ Transplantation

H. H. Hirsch[1,2,*], P. Randhawa[3] and the AST Infectious Diseases Community of Practice

associated nephropathy [PyVAN] in 1–10% of kidney transplant patients [1–4] and polyomavirus-associated

BKV screening methods

Screening method	Positive predictive value (%)	Negative predictive value (%)	Sensitivity (%)	Specificity (%)
Decoy cells [8]	29	100	25	84
Haufen [35]	97	100	100	99
BK urine PCR [8, 36, 37]	40	100	100	78
BK serum PCR [8, 36, 37]	50–60	100	100	88

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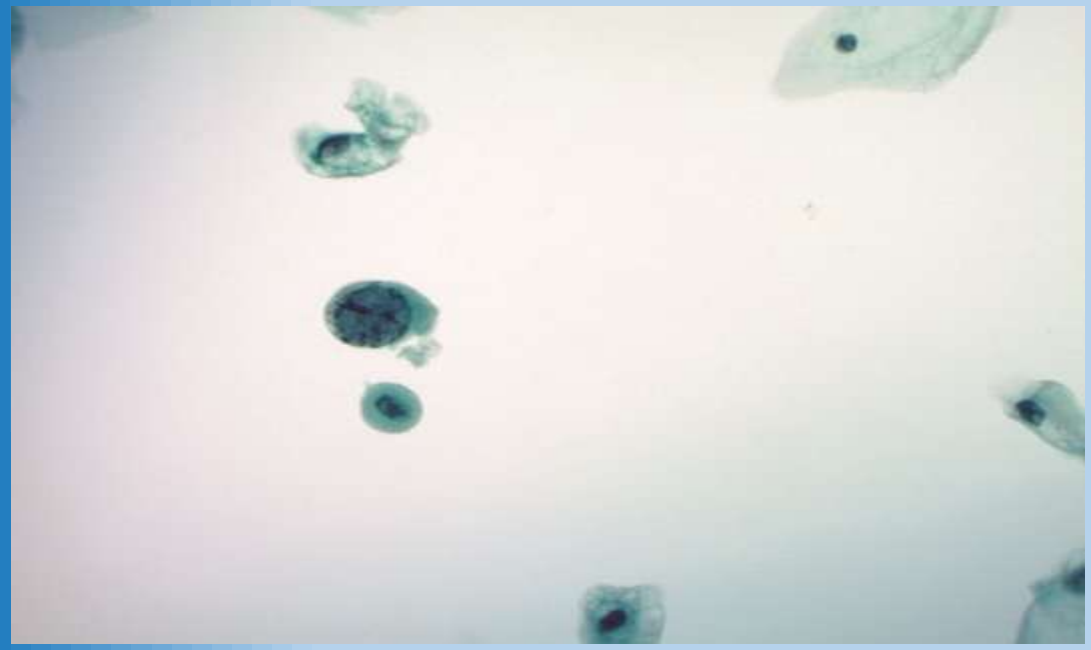
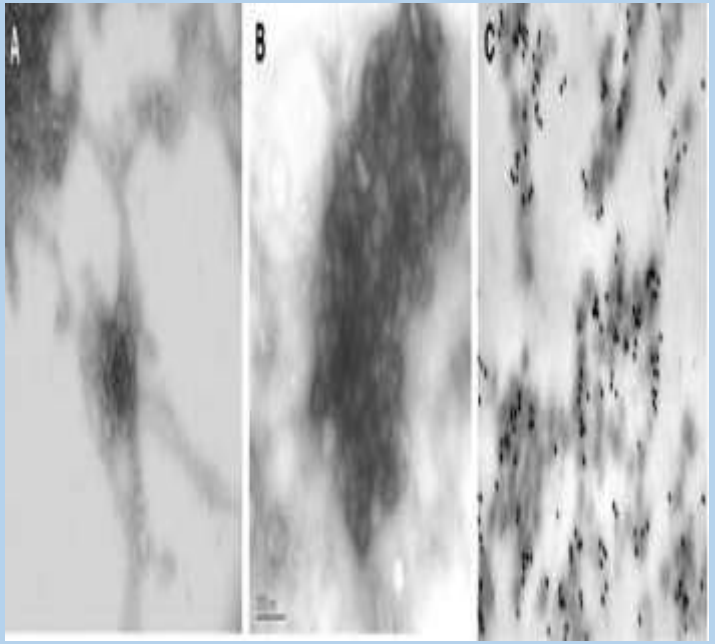
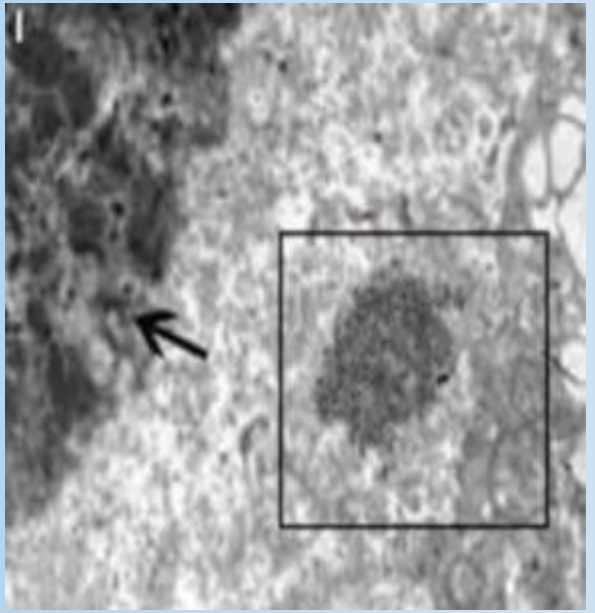
Urine







Urine cytology for polyomavirus inclusion-bearing "decoy cell" infected cells is an enlarged nucleus with a single large basophilic intranuclear inclusion

Three-dimensional, cast-like, dense polyomavirus aggregates and Tamm-Horsfall protein in urine samples analyzed by EM.

CLINICAL RESEARCH www.jasn.org

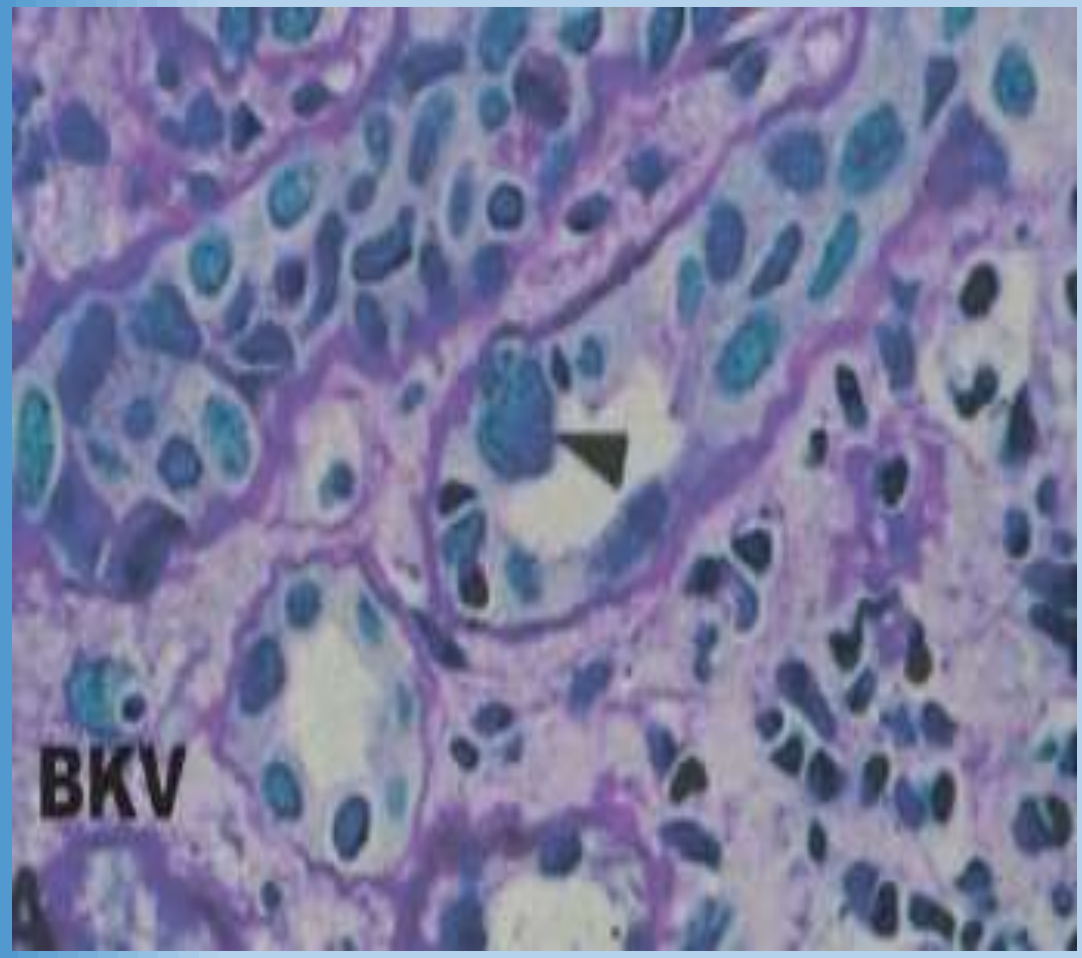
Presence of Urinary Haufen Accurately Predicts Polyomavirus Nephropathy

Harsharan K. Singh,* Kenneth A. Andreoni,† Victoria Madden,* Karin True,*

Blood

- BK detection by real-time PCR of plasma is very sensitive and specific for the development of BKVN.
- This is the preferred screening method at most transplant centers .
- A definitive viral load cutoff associated with nephropathy has not been established, but retrospective studies have suggested that a BK viral load >4 log copies/mL is strongly associated with finding BKVN on biopsy .

Hirsch HH, et al. Transplantation 2005; 10: 1277–1286



Some tubular epithelial cells exhibit finely granular and markedly enlarged nuclei with a ground glass appearance (arrowhead) .
Immunohistochemical staining for SV40 T antigen demonstrates numerous nuclei of tubular epithelial cells in tubular profile with reaction product

BK histology grading systems

BKVN stage	University of Maryland (2001) [46]	American Society of Transplantation (2013) [21]	Banff working proposal (2009) [45]
Stage/Class A	-Any degree of viral infection/cytopathic changes -Any degree of tubular injury -No inflammation	-Viral infection/cytopathic changes <25% -Interstitial inflammation <10% -Tubular atrophy <10% -Interstitial fibrosis <10%	-Viral infection detected -Minimal tubular epithelial cell lysis -No acute tubular necrosis -Chronicity score <ci3 and <ct3
Stage/Class B	-Any degree of viral infection/cytopathic changes -Any degree tubular injury -Inflammation <25->50%	-Viral infection/cytopathic changes 11–50% -Interstitial inflammation 11–50% (B1 11–25%, B2 26–50% and B3 >50%) -Tubular atrophy <50% -Interstitial fibrosis <50%	-Viral replication in cortex or medulla -Tubular epithelial cell lysis -Viral acute tubular necrosis -Chronicity score <ci3 and <ct3
Stage/Class C	-Any degree of viral infection/cytopathic changes -Any degree of tubular injury ->50% tubular atrophy or fibrosis	-Variable viral infection/cytopathic changes -Variable inflammation -Tubular atrophy >50%	-Viral replication in cortex or medulla -Chronicity score = ci3 and ct3

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BK virus infection: an update on diagnosis and treatment

Deirdre Sawinski and Simin Goral

Treatment strategies for BKV and BKVN

Treatment	Reference	Immunosuppression adjustment strategy	Patients with BKV or BKVN	Outcome	Adverse events
Immunosuppression reduction	Hirsch *et al.* [8]	Varied; CNI minimization or switch of agent	5	4/5 cleared BKV	-Three episodes of rejection -No allograft losses to BKVN
	Almeras *et al.* [57]	CNI and MMF dose reduction simultaneously	11	8/11 cleared BKV	-Three episodes of rejection -No allograft losses to BKVN
	Weiss *et al.* [58]	Withdrawal of CNI or MMF versus dose reduction of both CNI and MMF	35	19/35 retain allograft function	-CNI withdrawal is associated with superior allograft survival compared with dose reduction strategy
	Schaub *et al.* [33]	CNI minimization followed by discontinuation of MMF	38	35/38 cleared BKV	-Three episodes of acute rejection -No graft losses due to BK -No difference in patient or kidney survival with BK
	Hardinger *et al.* [59]	MMF discontinuation followed by minimization of the CNI	23	12/23 cleared BKV	-Five episodes of acute rejection -No graft losses due to BK -Patient survival was inferior in the BK group, but allograft survival was similar
Leflunomide	Faguer *et al.* [60]	MMF replaced with leflunomide	11	5/11 cleared BKV	-One episode of acute rejection -One graft lost to BKVN
	Leca *et al.* [61]	MMF replaced with 'low-dose' or 'high-dose' leflunomide	21	11/21 cleared BKV	-Four graft losses
Cidofovir	Kuypers *et al.* [62]	MMF/CNI reduction with/without 'adjuvant' cidofovir	21	6/8 cidofovir patients cleared BKV	-Two acute rejections in the cidofovir group -No graft losses in the cidofovir group

TREATMENT

➢1-Reduction of immunosuppression :

- Is the mainstay of BKVN treatment.
- Management approaches differ (discontinuation of the anti-metabolite, dose reduction of the calcineurin inhibitor (CNI) by 25–50% targeting significantly lower levels (tacrolimus 3–4 ng/mL and cyclosporine 50–100 ng/mL, or even less) or switching from tacrolimus to cyclosporine .

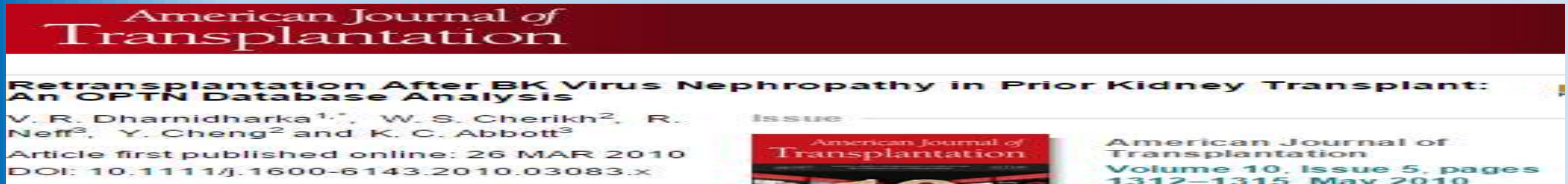
•2- Other treatment alternatives :

- (leflunomide, cidofovir, ciprofloxacin, rapamycin or intravenous immunoglobulin).

Johnston O, et al. Transplantation 2010

RETRANSPLANTATION

- Retransplantation after allograft loss due to BKVN is a reasonable option.
- Of the 126 retransplants, only one kidney was lost due to recurrent BKVN.
- One- and 3-year allograft survival in the retransplanted patients was excellent at 98.5 and 93.6%, respectively.
- Pretransplant clearance of BK viral load is necessary.
- Transplant nephrectomy in patients with failed graft due to BKVN has not been found protective after retransplantation.


American Journal of Transplantation

Retransplantation After BK Virus Nephropathy in Prior Kidney Transplant: An OPTN Database Analysis

V. R. Dharnidharka[1,*], W. S. Cherikh[2], R. Neff[3], Y. Cheng[2] and K. C. Abbott[3]

Article first published online: 26 MAR 2010

DOI: 10.1111/j.1600-6143.2010.03083.x

Issue

American Journal of Transplantation

American Journal of Transplantation
Volume 10, Issue 5, pages 1312–1315, May 2010

PARVOVIRUS B19

Parvovirus B19 and the Kidney

Clin J Am Soc Nephrol 2: S47–S56, 2007.

Meryl Waldman and Jeffrey B. Kopp

Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

- Parvovirus B19 is a small, non enveloped, single stranded DNA virus that was discovered in 1975 and first linked with human disease in 1981 .

- Infection with parvovirus is very common and occurs worldwide Acquisition is often during childhood .

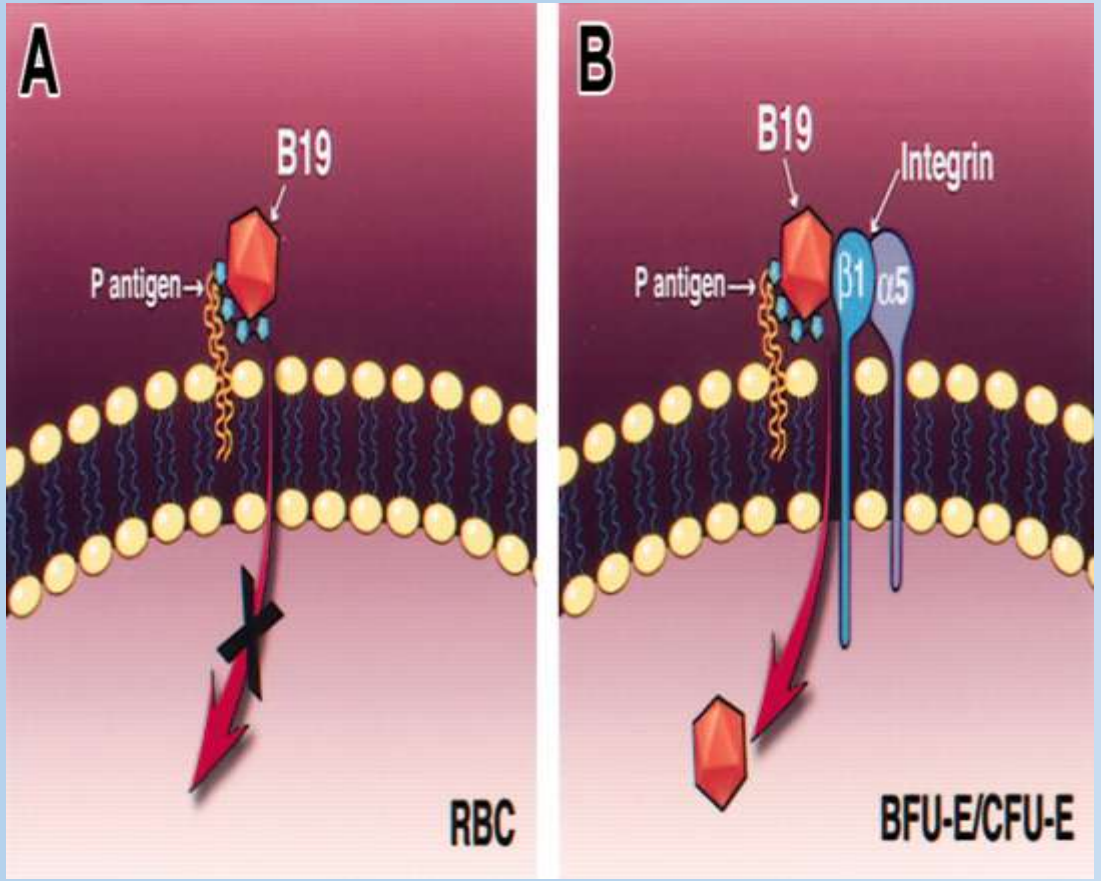
- The human parvovirus B19 is divided into three genotypes (B19, LaLi-like, and V9-like) which have 10% nucleotide divergence .

Transmission of infection

- Inhalation of virus in aerosol droplets .
- Vertically from mother to fetus .
- Transfusion of blood products .
- Bone marrow transplants.
- Solid-organ transplants .

Pathogenesis and Immune Response

- B19 targets the erythroid progenitors in the bone marrow by binding to the glycosphingolipid globoside (P antigen) .
- P antigen is expressed abundantly on erythroblasts .
- Recent studies support the existence of a cellular co-receptor, 51 integrin, for successful infection , although this remains controversial.



Clinical syndromes B19 infection

Well-Established Syndromes	Other Associations Based on Organ System
Fifth disease Arthropathy Hydrops fetalis, intrauterine fetal death, miscarriage (after maternal infection during pregnancy) Transient aplastic crisis (in patients with chronic hemolytic disorders) Chronic pure red blood cell aplasia (in immunocompromised patients)	Renal: Proliferative glomerulonephritis (46–49,51,52,58–60), collapsing glomerulopathy (50,53,88), FSGS (55,61), thrombotic microangiopathy (56), renal transplant dysfunction (82,83), acute allograft rejection (81) Rheumatic: Rheumatoid arthritis, systemic lupus erythematosus, chronic fatigue syndrome, dermatomyositis, uveitis, systemic sclerosis (reviewed in reference [98]) Cardiac: Myocarditis (99), cardiomyopathy (99), diastolic dysfunction (100) Hepatobiliary: Hepatitis (101), fulminant liver failure (102) Hematologic: Hemophagocytic syndrome (103), idiopathic thrombocytopenic purpura (104), hemolytic uremic syndrome (62) Dermatologic: "Gloves and socks" syndrome (41), Gianotti-Crosti syndrome (98), erythema nodosum (41) Vasculitis: Kawasaki disease (105), Henoch-Schönlein purpura (54,63), microscopic polyarteritis nodosa (62), Wegener's granulomatosis (64) Neurologic: Encephalopathy, meningitis, seizures, transverse myelitis, Guillain-Barré syndrome, acute cerebellar ataxia, neuropathy (reviewed by Barah *et al.* [106]) Pulmonary: Idiopathic pulmonary fibrosis, scleroderma-associated pulmonary fibrosis, lymphocytic interstitial pneumonitis, septal capillaritis (107)

Meryl Waldman and Jeffrey B. Kopp Clin J Am Soc Nephrol 2: S47–S56, 2007

Glomerular Diseases Associated with Parvovirus

- **Acute nephritic syndrome with hypocomplementemia often following a prodrome of fever, rash, and arthritis is most common .**
- **Nephrotic syndrome:**
- **Several case reports in patients with sickle cell disease.**
- **Histologic features shows pattern that is consistent with acute postinfectious glomerulonephritis.**

Komatsuda A, *Am J Kidney Dis* 36: 851–854, 2000

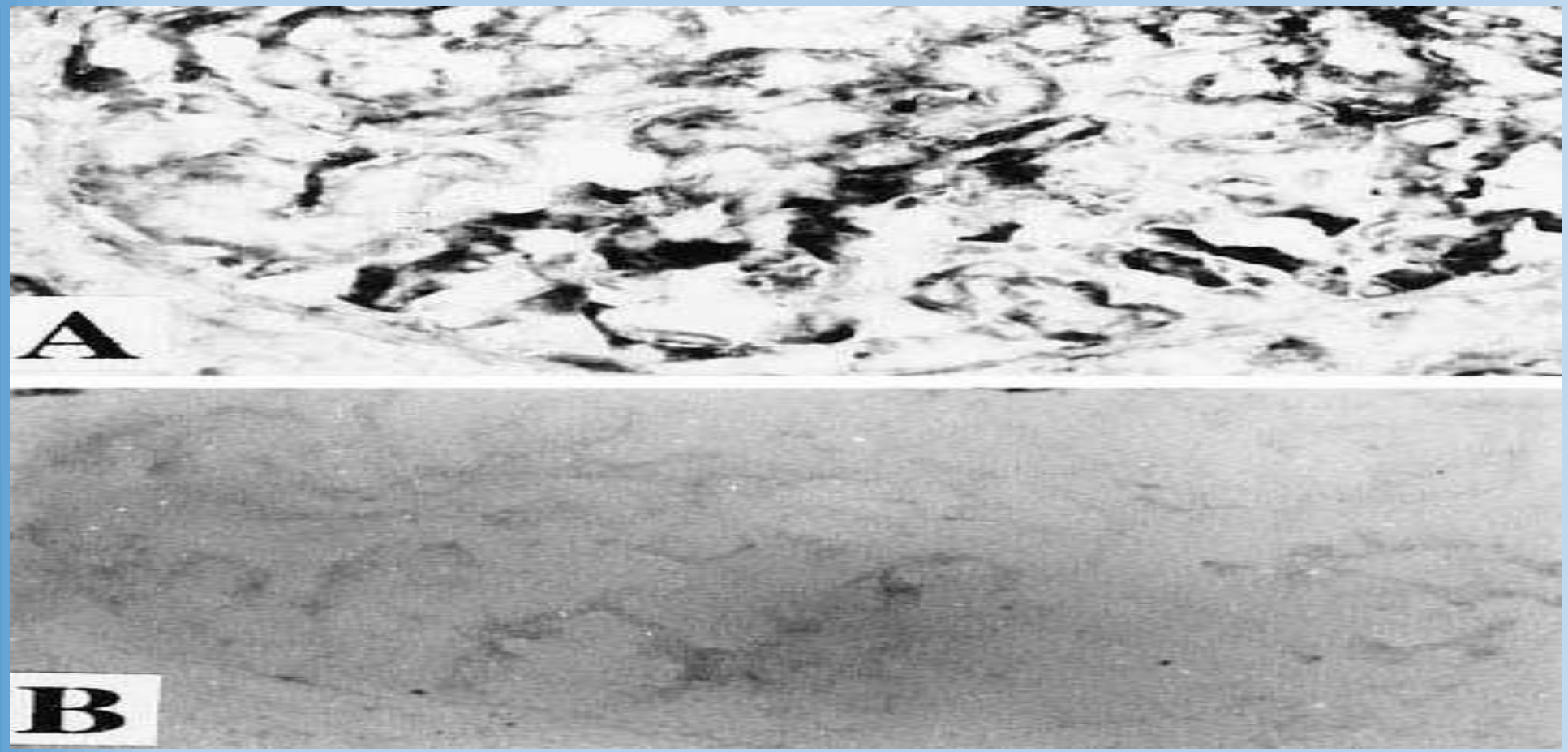
- **Thrombotic microangiopathy , Hemolytic uremic syndrome**
- **Spontaneous recovery is common, but some have persistent renal dysfunction and/or proteinuria.**

Wierenga KJ *Lancet* 346: 475–476, 1995

Endocapillary Proliferative Glomerulonephritis in a Patient With Parvovirus B19 Infection

Atsushi Komatsuda, MD, FJSIM, Hiroshi Ohtani, MD, Takashi Nimura, MD, FJSIM, Akihiko Yamaguchi, MD, Hideki Wakui, MD, Hirokazu Imai, MD, FJSIM, FACP, and Akira B. Miura, MD

American Journal of Kidney Diseases, Vol 36, No 4 (October), 2000: pp 851-854



Immunohistochemical localization of HPV antigen in renal biopsy sections.

Parvovirus Infection in Dialysis Populations

- The impact and role of parvovirus B19 infection in patients with chronic kidney disease or ESRD is not known.
- Nevertheless, there are several reasons to think that parvovirus may be an important pathogen in these populations.
- For most patients, erythropoiesis is maintained by erythropoiesis-stimulating agents, and red blood cells may have a shortened life span in the setting of uremia.
- Administration of erythropoietin during B19 infection can facilitate viral replication by providing new target cells , thereby prolonging viremia and its associated complications.

Arzouk N, *Transpl Int* 19: 166–169, 2006

Parvovirus in Kidney Transplant Recipients

- There is often a lack of classical B19-associated symptoms, such as rash and arthritis, that could provide clues to the diagnosis.
- Both acute anemia and chronic pure red blood cell aplasia are the most frequently reported .
- The diagnosis of B19-associated anemia in this population can be challenging .
- Anemia is relatively common after transplantation, particularly in the early posttransplantation period, and can be multifactorial.
- Other clinical complications include liver dysfunction , fibrosing cholestatic hepatitis , encephalitis , and cerebral vasculitis .

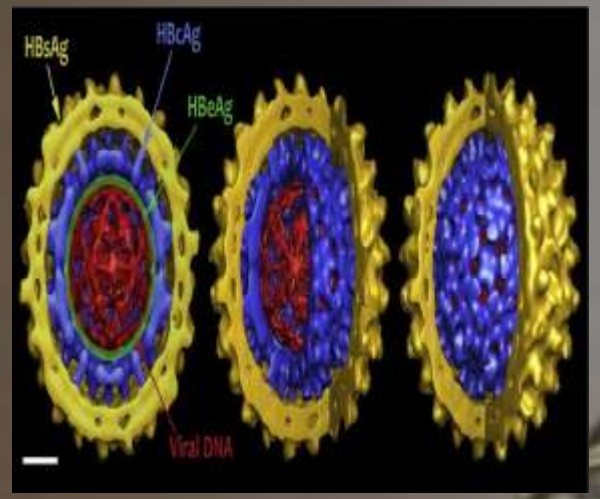
- Cavallo R, et al.J Clin Virol 26: 361–368, 2003

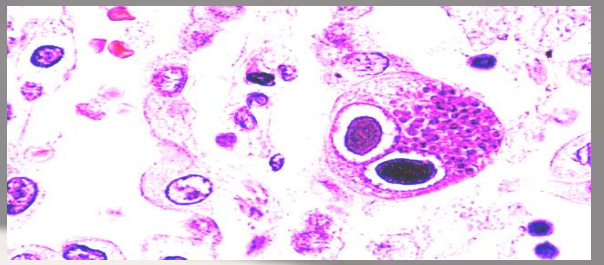
Treatment

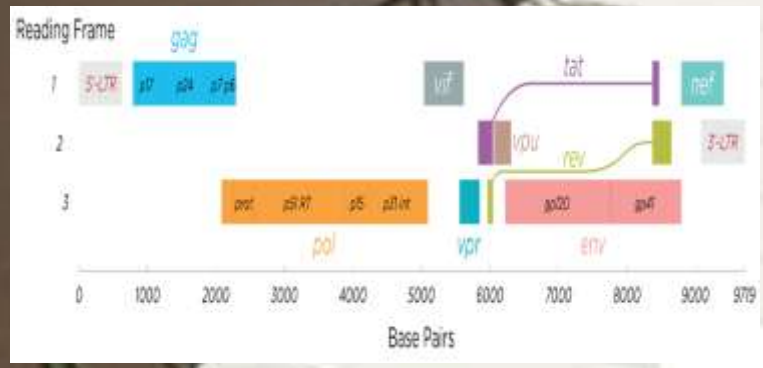
- Specific antiviral therapy is not available to treat B19 infection.
- Most cases of infection in immunocompetent hosts do not need treatment .
- 1- Commercial Ig (IVIG) :
- No much controlled studies have been carried out
- 400 mg/kg per d for 5 to 10 consecutive days seems to be clinically useful .
- 2- Reduction of immunosuppressive medication :
- is often recommended in addition to IVIG .
- Several reports have concluded that symptomatic B19 infection is linked specifically to the use of tacrolimus rather than the overall state of immunosuppression.

Geetha D, et al :.*Clin Transplant* 14: 586–591, 2000

Choi SH, et al :. *Scand J Infect Dis* 34: 71–75, 2002


HBsAg
HBcAg
HBeAg
Viral DNA




Reading Frame
gag
1
2
3
5'-LTR
p17
p24
p7p6
vif
tat
nef
vpu
rev
3'-LTR
prot
p51 RT
p15
p31 int
gp120
gp41
pol
vpr
env
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
9719
Base Pairs

CONCLUSION

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- Diverse mechanisms of glomerular and tubulointerstitial injury and heterogeneous clinicopathologic patterns underlie the relationship between viral infection and glomerular disease.
- The etiological role of some viruses is still undefined.
- Molecular biology techniques are vital in elucidating the precise location and role of viruses in the pathogenesis of virus-related nephropathy.
- Some of the pathogenic mechanisms and molecules underlying viral nephropathy are direct cytopathogenic effects on glomerular and tubulointerstitial cells, circulating immune complexes, hemodynamic perturbation and rhabdomyolysis .
- Different viruses cause different forms of nephropathy .

Thanks for your attention!

Ganciclovir-resistant CMV

- Currently, the incidence of ganciclovir-resistant cytomegalovirus in kidney transplant recipients is estimated to be 0.54-1% .
- One of the main causes of resistance is a mutation of UL97 protein.
- Maribavir (MBV) which is an orally administered potent inhibitor of the CMV UL97 kinase

Avery RK, et al .Transplant Infectious Disease 2010; 12 (6): 489-96.

- Leflunomide There are some case reports that proved success of treatment of multiresistant CMV infections by leflunomide .

Levi ME, et al. Transplant Infectious Disease 2006; 8 (1): 38-43.

- A novel anti-CMV (AIC246) :
- Targets the viral terminase complex .
- The first successful case of CMV treated with this compound.

Kaul DR, et al. American Journal of Transplantation 2011; 11 (5): 1079-84.